A magnetic resonance imaging, histological, and dose modeling comparison of focused ultrasound, radiofrequency, and Gamma Knife radiosurgery lesions in swine thalamus

Laboratory investigation

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Object. The purpose of this study was to use MRI and histology to compare stereotactic lesioning modalities in a large brain model of thalamotomy.

Methods. A unilateral thalamotomy was performed in piglets utilizing one of 3 stereotactic lesioning modalities: focused ultrasound (FUS), radiofrequency, and radiosurgery. Standard clinical lesioning parameters were used for each treatment; and clinical, MRI, and histological assessments were made at early (<72 hours), subacute (1 week), and later (1–3 months) time intervals.

Results. Histological and MRI assessment showed similar development for FUS and radiofrequency lesions. T2-weighted MRI revealed 3 concentric lesional zones at 48 hours with resolution of perilesional edema by 1 week. Acute ischemic infarction with macrophage infiltration was most prominent at 72 hours, with subsequent resolution of the inflammatory reaction and coalescence of the necrotic zone. There was no apparent difference in ischemic penumbra or “sharpness” between FUS or radiofrequency lesions. The radiosurgery lesions presented differently, with latent effects, less circumscribed lesions at 3 months, and apparent histological changes seen in white matter beyond the thalamic target. Additionally, thermal and radiation lesioning gradients were compared with modeling by dose to examine the theoretical penumbra.

Conclusions. In swine thalamus, FUS and radiosurgery lesions evolve similarly as determined by MRI, histological examination, and theoretical modeling. Radiosurgery produces lesions with more delayed effects and seemed to result in changes in the white matter beyond the thalamic target.

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Key Words • focused ultrasound • radiofrequency • radiosurgery • Gamma Knife • thalamotomy • radiation dose • thermal dose • functional neurosurgery • stereotactic radiosurgery

The human brain was first targeted with deep-seated, electrolytic lesions of the medial thalamus for the treatment of mental disorders in the late 1940s.8,59 Since then, various lesioning modalities have been successfully used, including direct anodal current,61 heat,31 cold,11 alcohol,10,12,47 and radiofrequency.2,62 Ultrasound lesioning of brain was developed in the 1950s to create deep brain lesions,23,24 but it was eventually abandoned because of the need for a craniotomy and acoustic window.25,44,48

Abbreviations used in this paper: CEM = cumulative equivalent minute; FUS = focused ultrasound; GFAP = glial fibrillary acidic protein; GKRS = Gamma Knife radiosurgery; LFB = Luxol fast blue.

Today, stereotactic radiofrequency lesioning represents the standard of care for surgical ablation of deep brain structures, while stereotactic radiosurgery is reserved for patients who require a “noninvasive” approach. These forms of stereotactic lesioning have proven effective for movement disorders and other neurological diseases, but lesioning surgery has fallen out of favor twice, first with the advent of medical therapies24,26 and more recently in favor of implanted neurostimulator devices.5 However, some patients are unsuited for invasive deep brain stimulation therapy and could benefit from a...
less-invasive lesioning procedure that permits immediate evaluation of clinical efficacy.

Recent advances in ultrasound transducer technology have enabled transcranial sonication to be precisely focused to deep targets in the brain with MR guidance and temperature monitoring, avoiding the superficial burns that were noted in earlier studies. In fact, the first human trials for treatment of glioma and neuropathic pain have proven that FUS can be delivered through the intact human skull to heat targets and even ablate them with precision. Detailed aspects correlating the imaging and histological characteristics of FUS lesioning remain incompletely understood, especially in comparison with radiofrequency and radiosurgery lesions. In this large-animal study, thalamic lesion evolution over a 3-month period is examined for FUS, radiofrequency, and radiosurgery lesions.

**Methods**

**Experimental Design**

This study was approved by the Institutional Care and Animal Use Committee at the University of Virginia. Twenty-eight female piglets (Sus scrofa domesticus) weighing between 13 and 20 kg were divided into 3 lesioning cohorts. Each animal was treated with a unilateral stereotactic thalamotomy using MR-based targeting with a swine atlas and one of the following lesioning modalities: FUS, radiosurgery, or radiosurgery. Lesioning parameters for each specific modality were based on standard clinical practice for a thalamotomy procedure: FUS, energy required to achieve a maximum voxel temperature of 55°C–60°C; radiofrequency, 72°C × 60 seconds; and radiosurgery, 130 or 160 Gy.

Each cohort was assessed by means of MRI and histological examination at early (< 72 hours), subacute (1 week), and late (1–3 months) time points, except that early assessments of the radiosurgical group were omitted (Table 1).

**MRI-Guided Focused Ultrasound**

The procedures were performed at the University of Virginia Focused Ultrasound Surgery suite, which houses a clinical grade, 3-T MRI unit (GE Healthcare) combined with a 1024-element ultrasound transducer operating at 710 kHz (InSightec ExAblate Neuro).

**Transcranial Sonications.** Initially, 3 young animals were sonicated through an intact skull. This model required high acoustic energies to produce a lesion as the ultrasound focus and power transfer were impeded by the flat morphology of the swine cranium and a relatively poor fit within the hemispherical transducer array. Transcranial sonication was thus abandoned in favor of a craniectomy model in which appropriate target temperatures could be achieved.

**Cranietomy Sonications.** Following general anesthesia with inhalational isoflurane and intubation, the scalp was shaved and prepared so that a U-shaped incision could be reflected caudally to expose the cranium. A craniectomy was performed with a high-speed drill and rongeurs to expose both convexities of the brain while leaving the dura intact. Once the scalp was closed, normal saline was injected into the epidural space and subgaleal air was aspirated for more efficient ultrasound transmission.

The animal was transported from the vivarium to the FUS suite, where it was positioned on the MRI table for a high-resolution, baseline brain MRI study using a head coil. Once these planning images had been obtained, the animal was repositioned on its back with the head affixed and resting over the concave transducer, which was filled with chilled and degassed water. MR imaging using a body coil was obtained with the animal in this position over the cranial transducer array and fused to the MRI obtained with the head coil so that targeting could be performed to the swine homolog of the ventrolateral thalamus.

Low-power sonications were delivered to produce small (1°C–2°C) temperature rises sufficient to confirm target site with MR thermometry. Following anatomical confirmation of focus, we used a series of sonications of increasing power and/or duration to achieve a peak voxel temperature of 55°C–60°C (Table 2). Before the animal was transported back to the vivarium for extubation and recovery, high-resolution imaging was performed by removing the ultrasound transducer for MRI acquisition with a head coil.

**Radiofrequency Lesioning**

Following induction of general anesthesia with inhalational isoflurane and intubation, a stereotactic frame was positioned and a preoperative 3-T MRI study was performed. A twist drill hole was then made in the cranium so that a lesioning electrode with a 1.1-mm diameter and 4-mm exposed tip (Stereotactic TC Electrode, Cosman Medical) was stereotactically inserted to the ventrolateral thalamic target. A single lesion was made at 72°C for 60 seconds with a Radiomics RFG-3C generator. The electrode was then removed, and the incision was closed with nylon suture. The animal was transported for an immediate postoperative MRI and then to the vivarium for recovery.

**Gamma Knife Radiosurgery**

Each animal was intubated and placed under isoflurane general anesthesia. A Leksell stereotactic frame (Elekta) was mounted, and then the fiducial localizer box was placed. A stereotactic 3-T MRI study was performed, and the images were imported into the Gamma Knife
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TABLE 2: Thermal lesioning parameters∗

<table>
<thead>
<tr>
<th>Modality</th>
<th>Final Sonication</th>
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<td>6</td>
</tr>
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</tr>
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<td></td>
<td>mean</td>
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<td>radiofrequency</td>
<td>60</td>
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∗ Temp = temperature.

workstation. Dose planning was done with Elekta GammaPlan software using a single 4-mm isocenter placed in the ventrolateral thalamus. To cover the clinical range of dose used for GKRS thalamotomy, 2 animals received a maximum dose of 160 Gy to the target, and the other 2 animals were treated with 130 Gy. Radiosurgery was performed using the Gamma Knife Perfexion. The frame was removed following the treatment, and the animals were extubated and recovered in the vivarium.

Clinical Assessment

Animals were monitored for behavior, weight, and food intake by trained veterinary staff. A modified Tarlov score was used for clinical assessment in the posttreatment period.63 This scale has been used in ischemia and spinal cord injury studies to assess neurological function and is scored as follows: 0, no voluntary hind-limb function; 1, only perceptible joint movement; 2, active movement but unable to stand; 3, able to stand but unable to walk; 4, normal hind-limb motor function.

Magnetic Resonance Imaging

For MRI assessments, all animals were intubated and placed under general anesthesia using isoflurane. The sequences used for 3-T MRI (GE Healthcare) were as follows: T1-weighted, T2-weighted, FLAIR, gradient echo, diffusion weighted, and gadolinium-enhanced T1-weighted imaging.

Volumetric assessments of the lesions were also made from each MRI time point. The T1- and T2-weighted series were converted to ANALYZE format using MRicro.55 Lesion volumes were estimated using voxel-based intensity measurements for each time point in the survival period.

Histological Examination

After harvesting, the animal brains were fixed in 10% formalin for at least 3 weeks. Coronal sectioning was performed using the MRI scan obtained at the time point of euthanasia for guidance. Gross findings were photographed. The lesions were then sampled for histopathological examination. Paraffin-embedded 5-μm-thick sections were evaluated after H & E staining in all cases. Additional staining was performed in selected cases, including LFB for myelin and immunohistochemical staining for GFAP. Immunohistochemical analysis was attempted for C4d complement and MAP2 staining but there was no cross-reactivity with these immunomarkers utilizing antihuman antibodies.

Modeling of the Ultrasonic Thermal Dose Profile

Simulations were performed to estimate the thermal dose profile induced by ultrasound. The temperature increase was calculated by a finite-difference code based on discretization of the bioheat equation:50

$$\rho C_p \frac{\partial T}{\partial t} = \nabla (k \nabla T) + Q$$

where $\rho$ is the brain tissue density and $C_p$ its heat capacity; $k$ the brain tissue thermal conductivity. $\nabla (k \nabla T)$ models the thermal diffusion. $Q = \alpha p^2/2pc$ models acoustical power deposition, where $\alpha$ and $c$ are the tissue absorption coefficient and the speed of sound, respectively, and $p$ is the peak pressure amplitude. The 3D pressure field is calculated based on the geometry of the hemispherical 710-kHz array with a radius of curvature of 15 cm. The ultrasonic power used in the simulation was adjusted to obtain the mean temperature elevation in the brain observed in the pigs who underwent FUS after craniectomy pigs (Table 2). The parameters used in the computation are summarized in Table 3.18 Three-dimensional maps of temperature elevation were thus computed as a function of time during and after ultrasonic sonication.

Thermal dose was introduced by Sapareto and Dewey to assess thermal damages induced in living tissues.57 For each location and history of temperature, the thermal dose, or cumulative equivalent minute (CEM) is defined as the equivalent time that the temperature of reference of 43°C should be applied to obtain the same thermal damage:

$$CEM_{43} = \int_0^t R^{43-T(t)} dt$$

$$R = \begin{cases} 0.25 & \text{if } T < 43°C \\ 0.5 & \text{if } T > 43°C \end{cases}$$
TABLE 3: Parameters used in the simulation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<td>ρ</td>
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</tr>
<tr>
<td>Cp</td>
<td>3600 J·K⁻¹·kg⁻¹</td>
</tr>
<tr>
<td>k</td>
<td>0.54 W·K⁻¹·m⁻¹</td>
</tr>
<tr>
<td>α</td>
<td>5.7 Np·m⁻¹·MHz⁻¹</td>
</tr>
<tr>
<td>C</td>
<td>1633 m·s⁻¹</td>
</tr>
</tbody>
</table>

Dose/survival responses have been studied and indicate that 25 CEMs are required (threshold) to induce damage in cat and dog brain.¹⁷ The 3D maps of temperature elevation were integrated in time to compute 3D maps of CEM. The spatial profile of the CEM distribution was then extracted.

**Modeling of the Radiofrequency Thermal Dose Profile**

The thermal dose profile of radiofrequency lesioning was calculated the same way, except that the acoustical power deposition term in the bioheat equation was replaced by radiofrequency power deposition.¹³

\[ Q = \alpha E^2 / 2, \]

where \( E \) is the amplitude of the electric field in tissue, and \( \alpha \) is the conductivity of tissue (set to 0.3 sec⁻¹) according to tissue.¹³ The electric field created by the 1.1-mm-diameter tip was calculated using open EMS (http://openems.de), a free and open electromagnetic field solver based on finite-difference time-domain method. The source voltage applied to the electrode was adjusted to reach a temperature of 72°C at the top of the electrode tip.

**Modeling of the Radiation Therapy Dose Profile**

The Gamma Knife radiation dose profile was modeled using an idealized collimation of each source, so that a single source with a collimated beam radius projects a top-hat beam profile at the isocenter.²² Such modeling has been shown to predict the diameter of the 50% isodose contour with a mean 3% error.²² To allow direct comparison with the ultrasonic thermal dose profile, the collimated beam radius has been set to correspond to the radius of the thermal isodose threshold (25 CEMs).

**Results**

**Magnetic Resonance Imaging**

Initially, FUS lesions are not readily apparent, demonstrating only subtle diffusion restriction and faint enhancement suggestive of blood-brain barrier disruption. By 48 hours after treatment, however, 3 concentric zones appear on T2-weighted sequences, representing necrosis (inner zones, Zones 1 and 2) and perilesional, vasogenic edema (outer zone, Zone 3). This perilesional edema subsided by 10 days, and the lesion size diminished with intrinsic T1 shortening. The lesion cavity collapses by 1 month, making the lesion difficult to visualize on MRI (Fig. 1). Throughout the study, there were no blood products evident on gradient echo imaging.

Imaging results in the radiofrequency cohort were similar to those in the FUS cohort, although in the radiofrequency cohort the lesions were more pronounced, with more marked inflammatory changes demonstrated by greater diffusion restriction, edema, and enhancement. Additionally, the electrode track could be appreciated with an occasional hemorrhagic component.

Gamma Knife radiosurgery is associated with a different evolution of imaging findings. Lesions were not apparent during immediate, acute, or subacute imaging. At 1 month, a slight T2 signal appeared at the target. Final lesions at 3 months (n = 3) were difficult to appreciate, with only slight intrinsic T1 shortening. There was no enhancement or restricted diffusion, and gradient echo sequences showed no blood products.

Volumetric measurements were easier to calculate from T2-weighted imaging than from T1 sequences and the T2-based measurements are depicted in Fig. 2. Necrotic lesion size (defined as Zone 1 + Zone 2) in both the FUS and the radiofrequency cohorts consistently peaked at 48–72 hours with mean volumes of 167 and 133 mm³, respectively. These lesions coalesced to barely perceptible volumes by 1 month. Perilesional edema was also maximal at 48–72 hours. The volume of Zone 3 was nearly twice as large with FUS lesions (298 vs 150 mm³), but with both types of lesions, perilesional edema completely resolved by 7–10 days. There was a lot of variability noted in the lesion volumes of the series, but the trends in the lesion maturation process were consistent. The cohort sizes were insufficient for statistical analysis. The evolution of radiosurgery lesion volume was not assessed due to the small size of the lesions at 3 months and lack of early MRI.

**Histopathological Findings**

The gross and microscopic findings of the brains submitted to FUS and radiofrequency treatment were quite similar and corresponded to infarct-like lesions at different phases of pathological reaction. Animals analyzed 48–72 hours after these ablation procedures showed grossly small, well-delineated lesions in the thalamus, measuring on average 4 x 4 mm in the largest dimensions. The histopathological findings were consistent with an acute ischemic infarction characterized by edema, vacuolation of the neuropil, and ischemic neurons and axonal swellings, with minimal inflammatory infiltration at 48 hours and increasing infiltration of macrophages at 72 hours (Fig. 3).

One week after the ablation procedures, the lesions were characterized by subacute infarction, with tissue necrosis, extensive macrophage infiltration with accumulation of foamy macrophages, and neovascularization (Fig. 4). At 1 month after the ablation procedures, the histopathological findings were consistent with a subacute infarction, with circumscription of the lesions, cystic formation, decreased inflammatory reaction with only mild macrophage infiltration at the edge of the cystic lesion, and reactive gliosis (Fig. 5). Finally, at 3 months, the lesions were barely visible on gross examination, and on microscopic examination they were characterized by dense fibrillary gliosis.

The cortex and surrounding brain otherwise appeared normal in the craniectomy FUS and radiofre-
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...quency groups, although the electrode track was readily apparent in the latter without complicating features of hemorrhage or infarction. In the 3 animals treated with transcranial FUS, thalamic lesioning was apparent and consistent with the lesion maturation process, although extensive dural and cortical injury occurred most likely from thermal injury while grossly sparing the scalp and skull (Fig. 6).

The GKRS lesions demonstrated distinct histopathological characteristics compared with FUS or radiofrequency lesions. Acute histological evaluation (during the first 72 hours) was not performed. Early infarction characterized by pyknotic neurons and neuropil edema was apparent at 1 week after GKRS (Fig. 7A and B). At 3 months (n = 3), poorly circumscribed lesions were grossly apparent (Fig. 7C–E). Histopathological evaluation showed subacute infarction with moderate inflammatory infiltration by macrophages and gliosis, which included bizarre, large astrocytes (Fig. 7F–H). Dystrophic calcification was present in the borders of the lesions (Fig. 7D and F). Edema and macrophage infiltration extended beyond the thalamic lesion and into the surrounding white matter and deep gray nuclei (Fig. 7I).

Clinical Assessment

There were no behavioral changes postoperatively, and all animals continued their normal pattern of feeding such that weight gain typically approximated 1–2 lb/day. All animals maintained a modified Tarlov scale score of 4 throughout the study. Incisions healed within 1 week of surgery without apparent evidence of scalp burns in the craniectomy FUS group.

Dose Profiles

Both thermal and radiotherapy doses exhibit a sharp falloff outside the target (Fig. 8). Given the average ultrasonic parameters used experimentally (Table 2; 57.5°C maximum temperature voxel measured by MRI for a 16-second-duration sonication), the 25-CEM isodose threshold corresponds to a 1.5-mm plateau in radius, with a sharp decrease to a negligible value at a distance of 2 mm from center. The radiotherapy profile was thus calculated with a collimated beam radius of 1.5 mm. A 90% dose diminution is observed at a distance of 9 mm from center on the radiation profile and 1.9 mm on the ultrasonic thermal profile. The 25-CEM isodose threshold of the radiofrequency ablation profile corresponds to a 2.3-mm

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Fig. 1. Evolution of the thalamic lesioning process depicted on T2-weighted coronal MR images obtained in the craniectomy FUS, radiofrequency (RF), and radiosurgery (RS) cohorts.

Fig. 2. Volumetric measurements during the maturation of FUS (solid) and radiofrequency (speckled) lesions (Zones 1 and 2) and surrounding edema (Zone 3) as determined from T2-weighted MRI. d = days.
plateau in radius, with a 90% dose diminution at a distance of 2.7 mm. The radiofrequency thermal dose profile falloff is similar to the ultrasonic one, but the plateau is larger, in agreement with a higher temperature elevation for a longer heating time (Table 2), corresponding to a higher thermal dose at focus.

Discussion

In this study, a unilateral stereotactic thalamotomy was made in a swine model with one of 3 lesional modalities—namely FUS, radiofrequency, or radiosurgery. The primary finding is that MRI and histological characteristics of FUS and radiofrequency lesions are similar throughout early, subacute, and late time periods. Radiosurgery lesions differ; less circumscribed and more indistinct lesions are evident at 3 months, and there is evidence for injury to white matter tracts beyond the confines of the thalamic lesion.

![Fig. 3. Early lesions (48 hours) produced by FUS (A–C) and radiofrequency (D–F). Both FUS and radiofrequency produced well-delineated acute infarctions characterized by central ischemic necrosis and surrounding edema (A, D, and E). The periphery of the lesions shows a moderate degree of vacuolization of the neuropil (B and E), axonal swelling (C), and ischemic neurons (F) with minimal inflammatory infiltration. LFB (A and D), H & E (B, C, E, and F); original magnifications ×20 (A, D, and E), ×100 (B), ×400 (C), and ×200 (F).](image)

![Fig. 4. Subacute lesions (1 week) produced by FUS (A–C) and radiofrequency (D–F). Subacute infarction with central necrosis and dense inflammatory infiltration was seen in both groups of animals. Better delineation of the infarcts (A, D, and E) than early lesions, intense macrophage infiltration (B, C, and E), and neovascularization (C and F) were characteristic of the lesions at this stage. All H & E; original magnifications ×20 (A and D), ×200 (B), ×400 (C and F), and ×100 (E).](image)
Thermal lesioning has theoretical advantages over ionizing radiation for tissue ablation, primarily because of the sharp gradient of effect for a lethal dose from temperature,\textsuperscript{17} as compared with a more graduated dose fall-off with radiosurgery (Fig. 8). Thermal dose has a nonlinear relationship to the temperature achieved, so small increments of heating can result in large increases of thermal dose even when the duration of treatment is brief.\textsuperscript{17} Brain is the tissue most sensitive to heating, with the lowest threshold for ablation.\textsuperscript{17,49} Even at 43°C, brain tissue can be damaged with a 50% probability at 17.5 minutes,\textsuperscript{42} and complete ablation likely occurs with 25 minutes of exposure.\textsuperscript{17} The 25-minute threshold corresponds to 100% thermal dose in Fig. 8, and the falloff correlates with the 2-mm-radius lesions observed on histological examination. Histopathological evaluation of human glioma tissue treated with high-intensity FUS has reportedly demonstrated this small perilesional penumbra measuring a few cells in diameter.\textsuperscript{54} Similarly, radiofrequency lesions have been shown to have a sharp demarcation from viable brain.\textsuperscript{65} Although theoretical modeling may indicate a difference between FUS and radiofrequency with respect to the perilesional penumbra, no such difference was demonstrated by MRI or histological examination in the current study. Diffusion-weighted MRI likely provides the best assessment of the ischemic penumbra, but this modality lacks the spatial resolution to accurately quantify the sharpness of the lesions where the difference between necrosis and viable tissue can be a few cells in thickness. Immunohistochemical analysis of penumbral regions in this study was limited by the lack of cross-reactivity to monoclonal antibodies.

Intracerebral hemorrhage is always a primary concern with stereotactic lesioning procedures, and noninvasive treatments avoid the risks associated with penetration of the brain by an electrode, although the risk of hemorrhage from target tissue ablation remains.\textsuperscript{56} We did not observe clinical, imaging, or histological morbidity from radiofrequency electrode insertion in this series. It is important to note that target readjustment in radiofrequency lesioning requires additional electrode penetrations with potentially reduced accuracy due to brain shifting.\textsuperscript{19} Focused ultrasound and radiosurgery targeting can be realigned in any dimension during the procedure without concern for movement of the brain, and FUS adjustments can be immediately verified with MRI before delivery of a therapeutic treatment. On the other hand, there is no limitation to the region of treatment with radiofrequency and radiosurgery, whereas FUS targeting is currently limited to the deeper regions of the brain where focusing and convergence of multiple acoustic beams occurs most optimally. Transcranial FUS lesioning of the cortex or superficial subcortical regions is not currently feasible with the limited treatment envelope of today’s multi-element, phased-array transducers.

The incidence of hemorrhage at the lesioned target was also investigated, as microhemorrhages have been histologically demonstrated in rabbits, swine, and primates with FUS lesions when temperatures have exceeded 60°C.\textsuperscript{9,41,42} Since a high probability for tissue ablation occurs when the tissue is briefly exposed to temperatures of approximately 55°C–60°C,\textsuperscript{57} our target FUS treatments were intended to reach these peak MR voxel temperatures. Ideally, the remainder of the target volume around the reported peak or hottest voxel from MR thermometry still receives lethal temperatures for effective lesioning, although the FUS lesions in this study were generally less pronounced on MRI. Radiofrequency lesioning depends upon the dissipation of heat from a central electrode to the lesion edge. The higher radiofrequency temperatures can be immediately verified with MRI before delivery of a therapeutic treatment. On the other hand, there is no limitation to the region of treatment with radiofrequency and radiosurgery, whereas FUS targeting is currently limited to the deeper regions of the brain where focusing and convergence of multiple acoustic beams occurs most optimally. Transcranial FUS lesioning of the cortex or superficial subcortical regions is not currently feasible with the limited treatment envelope of today’s multi-element, phased-array transducers.
lation/necrosis at much lower temperatures for less time. Despite the differences of peak temperatures and duration of treatment, FUS and radiofrequency lesions in this study were similar in size of necrosis, based on histological assessment and the absence of microhemorrhage at the target.

The MRI and pathological characteristics of radiofrequency lesions in this study appeared similar to those described in prior reports. Radiofrequency lesion volume has been shown to correlate with in vitro tests\textsuperscript{20} and contrast-enhanced T1-weighted imaging,\textsuperscript{43} but not necessarily with Zone 3 of perilesional edema demonstrated on T2-weighted sequences.\textsuperscript{43} Our MRI results suggested a more pronounced inflammatory reaction with radiofre-

Fig. 7. Subacute (1 week [A and B]) and late (3 months [C–I]) GKRS lesions. Early infarction, with edema and hypoxic-ischemic red neurons, was apparent 1 week after the procedure (A and B). Poorly circumscribed lesions were seen 3 months after the procedure (C–E). LFB staining shows irregular borders of the lesion (C) with extension of demyelination to the adjacent white matter (arrows) and edema of surrounding deep gray nuclei (asterisk). Higher magnification of edema is seen in Panel I. GFAP immunostaining highlights the extension of gliosis surrounding the lesion and in the adjacent gray and white matter (E). Intensive inflammatory infiltrates with dense macrophage reaction and dystrophic calcification (D and F, arrows) were present (D and E). Note extension of the macrophage infiltration into the surrounding white matter highlighted as negative profile by GFAP immunostaining (E, arrows). Additionally, large, bizarre astrocytes (G) were observed intermixed with the inflammatory infiltrates and highlighted by GFAP immunostaining (H). H & E (A, B, D, F, G, and I) and LFB (C); original magnifications $\times$100 (A and F), $\times$200 (B, G, and I), $\times$20 (C and E), $\times$40 (D), and $\times$400 (H).
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Fig. 8. Simulated ultrasonic thermal dose (unbroken line), radiofrequency thermal dose (dashed line), and GKRS dose (dashed-dotted line) profiles as a function of distance in tissue. Zero distance thus corresponds to the center of the ultrasonic beam, the center of the radiofrequency electrode, eq.min = CEM.

Conclusions

The MRI and histological characteristics of the lesions produced by MR-guided FUS in the swine thalamus are similar to those produced by traditional stereotactic radiofrequency lesioning. As a noninvasive modality, FUS seems to spare the overlying cerebral tissue from pathological changes beyond the focus of acoustic energy, although transcranial sonication is less efficient through the swine cranium. In this study, stereotactic radiosurgery was associated with white matter injury beyond the confines of the thalamic target.

Disclosure

This research was generously funded by the Focused Ultrasound Surgery Foundation. Matt Eames, Ph.D., from the Focused Ultrasound Surgery Foundation, assisted in the thermal dose calculations and with technical support during FUS experiments. The research was conducted independently from industry and without technical or financial input from InSightec, Elekta, Radionics, or Cosman Medical.

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